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Update on the role of copanlisib in hematologic malignancies

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***Abstract*:** Clinical research in hematologic malignancies is continually advancing with emerging concepts in therapy and evolving results from clinical protocols. Targeting of the PI3K pathway remains a valuable treatment across both hematologic and solid malignancies. There are currently four United States Food and Drug Administration (FDA)-approved PI3K inhibitors, with several others in development. Copanlisib is a pan-PI3K inhibitor currently FDA-approved for the treatment of relapsed/refractory follicular lymphoma (FL) following two lines of therapy. Since FDA approval, there have been further investigations into the long-term safety profile of copanlisib, as well as treatment of FL and other lymphoma subtypes, both indolent and aggressive. Here, we review the most recent available data from clinical trials, describe the management of the most common side effects, and explore future concepts. The use of copanlisib as part of a combination therapy for various hematologic malignancies will also be discussed. Copanlisib is a unique drug compared with other PI3K inhibitors, with remarkable potential to improve our armamentarium in cancer treatment.

Keywords: copanlisib, lymphoma, PI3K, targeted therapy

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Introduction

The PI3K/AKT/mTOR intracellular signaling pathway functions to regulate the cell cycle, with influences on cell proliferation, cell survival, and angiogenesis.[1] These functions have made the PI3K/AKT/mTOR pathway an important therapeutic target in the treatment of cancer.[2] Currently there are four United States (US) Food and Drug Administration (FDA)-approved PI3K inhibitors – idelalisib, duvelisib, alpelisib, and copanlisib – that target a varied combination of the four class I isoforms of the PI3K protein. Copanlisib was approved by the FDA for treatment of relapsed follicular lymphoma (FL) in September 2017 and carries "orphan designation" by the European Medicines Agency (EMA) for marginal zone lymphoma (MZL). Copanlisib inhibits all four PI3K isoforms (P110α, P110β, P110δ, and P110γ), with the highest selectivity for the PI3Kα and PI3Kδ isoforms. This selectivity proves important as these isoforms are commonly found in malignant B cells, namely chronic lymphocytic lymphoma (CLL) and diffuse large B cell lymphoma (DLBCL).[3] Use of copanlisib has expanded across the B cell malignancies and now includes investigations in the treatment of solid tumors.

Since the initial approval of copanlisib based on results from the CHRONOS-1 trial, there are published data from several other trials further demonstrating efficacy in B cell malignancies. Others have provided insight into potential biomarkers that may predict outcomes when using PI3K inhibitors, particularly copanlisib. Active clinical trials are exploring combinations of copanlisib with chemoimmunotherapy to further enhance efficacy. Additionally, there are extended data providing a better understanding of the unique toxicity profile. We aim to provide an updated review of copanlisib since the initial FDA approval.

PI3K inhibitors

PI3K plays a crucial role in cell proliferation and survival as well as oncogenesis.[4] The four isoforms of PI3K have differing presence across cell lines, with restriction of PI3Kδ to those of

hematopoietic origin, and are commonly found in B cell malignancies. In B cells, the PI3K pathway plays a role in B cell receptor (BCR) signaling.[5] The potent PI3Kδ inhibitor, idelalisib, has been shown to selectively induce apoptosis of CLL cells compared with other hematologic cell lines including T- and natural killer (NK)-cells.[6] Alternatively, copanlisib inhibits the catalytic activity of all four PI3K isoforms, with higher potency toward PI3Kα and PI3Kδ as mentioned above. PI3Kα and PI3Kβ have relatively ubiquitous expression in most cell types, with reports of PI3Kα potentially having an implication in relapse of disease. PI3Kγ and PI3Kδ are expressed mostly on hematopoietic tissues and serve better as a targeted approach to treating hematologic malignancies.[3,7–9] Other off-target effects of copanlisib may enhance the efficacy of the agent.[10] The higher efficacy on the PI3Kα and PI3Kδ isoforms and influences on the tumor microenvironment have made copanlisib an attractive agent with considerable differences compared with other available PI3K inhibitors.[11]

The dosing schedule and administration differs for the approved PI3K inhibitors. Both idelalisib and duvelisib are twice daily oral agents given until disease progression or unacceptable toxicity. Copanlisib is an intravenous drug administered weekly on days 1, 8, and 15 of a 28-day cycle. The infusion is a fixed dose of 60 mg and infused over 1 h. Some clinical trials have utilized a weight-based dosing from 0.4 to 0.8 mg/kg. No dose modifications are required for renal dysfunction; however, moderate hepatic impairment (Child–Pugh class B) carries a recommended dose reduction to 45 mg. There is no need for routine premedication prior to infusion. Treatment continues until disease progression or unacceptable toxicity. Of note, other PI3K inhibitors carry a black box warning regarding severe or fatal toxicities, involving diarrhea and colitis, cutaneous reactions, pneumonitis, hepatotoxicity, or opportunistic infections. Though copanlisib itself does not have a specific black box warning, the manufacturer still recommends use of Pneumocystis jiroveci pneumonia (PJP) prophylaxis during treatment.[12]

CHRONOS trials

The CHRONOS trial series is the original effort by Bayer, the manufacturer of copanlisib, to pursue drug approval in hematologic malignancies following the results of the safety/tolerability phase I protocol [ClinicalTrials.gov identifier: NCT00962611].[13] The results of the CHRONOS-1 trial are the basis for copanlisib FDA approval. The remaining three trials are ongoing, with limited reported data as accrual continues. The trials focus on the role of copanlisib in treatment of indolent B-cell non-Hodgkin lymphomas (NHL) and follow a stepwise introduction of copanlisib as monotherapy, in combination with rituximab, and finally in combination with standard chemoimmunotherapy regimens.

The phase II trial, CHRONOS-1 [ClinicalTrials.gov identifier: NCT01660451], is an open-label, uncontrolled trial using copanlisib monotherapy in patients with relapsed indolent or aggressive NHLs. The primary efficacy endpoint was overall response rate (ORR). Most patients had advanced stage disease at entry and had been heavily pretreated with a median of three lines of therapy. This large multicenter trial had two parts: Part A includes both indolent and aggressive B-cell lymphomas with weight-based dosing (0.8 mg/kg; maximum 65 mg) and Part B focused on indolent B-cell lymphomas with copanlisib fixed dose (60 mg). Patients received copanlisib IV infusion on days 1, 8, and 15 of a 28-day cycle.

CHRONOS-1 Part A enrolled 33 patients with indolent lymphoma and 51 patients with aggressive lymphoma. Indolent lymphoma subtypes included FL (FL grades 1 to 3a; 49%), CLL (40%), MZL (9%) and small lymphocytic lymphoma (SLL; 3%). Aggressive lymphoma subtypes included DLBCL (30%), mantle cell lymphoma (MCL; 22%), peripheral T-cell lymphoma (PTCL; 33%), transformed indolent FL (12%), and FL grade 3b (2%). Patients received at least two prior therapies, with a median number of four for the indolent lymphomas (range 2–10) and three for the aggressive lymphomas (range 2–9). The treatment duration was 5.7 cycles (22.7 weeks) for the indolent cohort and two cycles (8 weeks) for the aggressive cohort. The participants were ~50% male/female with a median age of 68 years in the indolent group and 63 years in the aggressive group. The ORR was noted to be 43.7% and 27.1% in the indolent and aggressive groups, respectively. The median progression-free survival (PFS) was 294 days (0–874 days) in the indolent group and 70 days (0–897 days) in the aggressive group.[14]

CHRONOS-1 Part B studied an additional 142 patients with lymphoma. A total of 141 patients enrolled with indolent lymphoma had a median age of 63 years (25–82 years) with relapsed or refractory indolent lymphoma who had received a median of three lines of therapy (range 2–9). Lymphoma subtypes included FL grade 1 to 3a (73%), MZL (16%), SLL (6%), and lymphoplasmacytic lymphoma (LPL; 4%). Patients were treated with the same dose and schedule of copanlisib as in Part A. An ORR of 60.6% was achieved compared with 59.2% from the original study, suggesting an improved response rate with time on treatment. The ORR in patients with FL was the same (58.7%), but the ORR in patients with MZL improved to 78.3%, with a low number of patients (2.1%) experienced progressive disease. The ORR of 60.6% included 16.9% with complete response (CR) was reported in the 2 year follow-up data, confirming a slight improvement in the initially reported 14.4% CR from the primary analysis. The median time to CR was 4.7 months, which was more than twice the median time to first response (1.8 months). The median duration of response (DOR) was 14.1 months (range 0.03–42.5) with a median follow up of 16.1 months. The median PFS was 12.5 months, and median overall survival (OS) was 42.6 months with a median follow up of 31.5 months. The 2 year OS rate was 69%.[15,16] The investigators separately published data regarding 23 MZL patients who received a median of 5.8 cycles with an ORR of 78% including three CRs (13%). The overall DOR was 17.4 months with median PFS 24.1 months.[17] In fact, copanlisib received US FDA Breakthrough Designation in May 2019 for the treatment of adult patients with relapsed MZL who have received at least two prior therapies based on this subset analysis from the CHRONOS-1 trial.[18] Furthermore, such positive results prompt researchers to explore the possibility of combining copanlisib and rituximab as a chemotherapy-free approach to newly diagnosed or relapsed MZL [ClinicalTrials.gov identifier: NCT03474744] (Table 1).

Based primarily on the results of CHRONOS-1 Part B, copanlisib received accelerated approval by the FDA for the treatment of relapsed FL in adults who have received at least two prior lines of therapy. The rate of adverse events (AEs) was low, and copanlisib was thus approved without a black box warning, unlike the other PI3K inhibitors. Even with the extended duration of monitoring, the incidence of treatment emergent AEs (TEAEs) remained almost unchanged compared with the original study, with the most common TEAEs being transient hyperglycemia (50.0%), diarrhea (35.2%), transient hypertension (29.6%), neutropenia (28.9%), pyrexia (26.8%), and fatigue (26.1%), with no new treatment emergent mortality. Noticeably, the highest incidence of AEs was seen early in the first 6 months as opposed to later on, suggesting that there is no evidence of cumulative toxicity.[15]

CHRONOS-2 [ClinicalTrials.gov identifier: NCT02369016] is a phase III study investigating copanlisib monotherapy in rituximab refractory indolent B-cell NHL. This randomized, double-blind, placebo-controlled protocol was opened at non-US sites. The trial is listed as active, not recruiting, and no results have been published to date.

CHRONOS-3 [ClinicalTrials.gov identifier: NCT02367040] is a phase III randomized, double-blind, placebo-controlled trial with the goal to evaluate copanlisib in combination with rituximab *versus* placebo plus rituximab in terms of PFS as the primary endpoint. Recruitment has completed, with 458 patients with relapsed indolent NHL (iNHL) who have received one or more lines of prior treatment. In the press release on 15 October 2020, Bayer announced that CHRONOS-3 has met its primary endpoint, and that safety and tolerability observed in the trial were generally consistent with previously published data on the individual components of the combination and no new safety signals were identified. The final publication containing CHRONOS-3 data is awaited.

CHRONOS-4 [ClinicalTrials.gov identifier: NCT02626455] evaluating copanlisib with standard chemoimmunotherapy [rituximab with bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine sulfate, prednisone)] in 551 patients with relapsed/refractory indolent NHL is currently active but not recruiting and the results were not available at the time of review submission.

[ClinicalTrials.gov identifier: NCT02391116]

The aggressive NHL DLBCL has two distant molecular subtypes based on cell of origin (COO), germinal center B cell-like (GCB), and activated

Table 1. Clinical trials with copanlisib in hematologic malignancies.

ClinicalTrials.gov identifier:	Phase	Intervention	Enrollment	Inclusion criteria	Primary endpoint	Status	Results
NCT01660451	II	Copanlisib	227	R/R NHL	ORR	Active, not recruiting	Dreyling *et al.*[14–16]
NCT02342665	Ib/II	Copanlisib	25	R/R iNHL	AEs ORR	Active, not recruiting	N/A
NCT02367040	III	Copanlisib (*versus* placebo) + Rituximab	458	R/R iNHL	PFS	Active, not recruiting	Pending
NCT02369016	III	Copanlisib	25	R/R iNHL	AEs	Active, not recruiting	Pending
NCT02535247	I/II	Pembrolizumab +/– Copanlisib	19	R/R T-cell or NK-cell lymphoma	PFS ORR	Active, not recruiting	N/A
NCT02626455	III	Copanlisib (*versus* placebo) + BR or R-CHOP	551	R/R iNHL	RP3D PFS	Active, not recruiting	N/A
NCT03052933	I/II	Copanlisib + Gemcitabine	28	R/R T-cell or NK-cell lymphoma	DLT/MTD ORR	Active, not recruiting	N/A
NCT03474744	II	Copanlisib + Rituximab	56	MZL	CR	Recruiting	N/A
NCT03484819	II	Copanlisib + Nivolumab	106	R/R DLBLC or PMBL	ORR	Recruiting	N/A
NCT03789240	II	Copanlisib + Rituximab	65	FL	CR	Recruiting	Lenz *et al.*[19,20]
NCT03877055	I/II	Copanlisib + Ibrutinib	45	R/R MCL	CR	Recruiting	N/A
NCT04155840	II	Copanlisib + BR	25	CLL/SLL	MRD	Recruiting	N/A
NCT04263584	II	Copanlisib + R-CHOP	80	DLBLC	PFS	Recruiting	N/A
NCT04433182	II	Copanlisib + BR	81	R/R DLBLC	PFS	Not yet recruiting	N/A
NCT04572763	I/II	Copanlisib + Venetoclax	N/A	R/R DLBLC	MTD ORR	Not yet recruiting	N/A

AE, adverse events; BR, bendamustine/rituximab; CLL/SLL, chronic lymphocytic lymphoma/small lymphocytic lymphoma; CR, complete response; DLBLC, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent NHL; MCL, mantle cell lymphoma; MRD, minimal residual disease; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; B-cell; ORR, overall response rate; PFS, progression free survival; PMBL, primary mediastinal large b-cell cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RP3D, recommended phase III dose; R/R, relapsed or refractory.

B cell-like (ABC), with differing gene expression profiles.[21] The ABC subtype tends to have *CD79B* mutations resulting in persistent activation of BCR signaling, in which PI3K plays an important role.[22] Coupled with *CD79B* and *MYD88* mutations, ABC subtypes may be more susceptible to inhibition of the PI3Kα and PI3Kδ isoforms.[23] Dual inhibition may be particularly important given feedback activation of PI3Kα seen in preclinical models for ABC cell lines treated with selective PI3Kδ inhibition.[24]

The use of copanlisib in the treatment of aggressive lymphomas, including DLBCL, has generated limited but encouraging data. The original phase I trial [ClinicalTrials.gov identifier: NCT00962611]

included three patients with unclassified DLBCL with a 33% ORR.[13] Part A of the phase II CHRONOS-1 trial [ClinicalTrials.gov identifier: NCT01660451] include 15 unclassified DLBCL patients with a single partial response (PR). These results, and the understanding of PI3K pathogenesis in DLBCL, prompted a non-US clinical trial. [ClinicalTrials.gov identifier: NCT02391116] is a single-arm, multicenter, phase II protocol evaluating the efficacy and safety of copanlisib monotherapy in patients with relapsed/refractory DLBCL. A total of 67 patients completed the trial enrollment goal. The trial included patients with *de novo* DLBCL and histologic transformation from FL. Investigators importantly separated patients by COO and *CD79B* mutation status to best identify candidates for treatment with copanlisib.[19,20]

The 67 treated patients included ABC subtype ($n=19$), GCB subtype ($n=30$), unclassifiable ($n=3$), and 15 patients with missing COO data. The reported ORR was 19.4% for all patients with 31.6% and 13.3% in the ABC and GCB DLBCL patients, respectively. The ORR results were further separated by *CD79B* mutation status with 22.2% in mutant *CD79B* ($n=9$) and 20% in wild-type *CD79B* ($n=45$). The overall median PFS was 1.8 months, and duration of response was 4.3 months. In general, the results demonstrated modest activity with an, as expected, numerically higher response rate in patients with ABC subtype DLBCL.[20] The findings support pursuing combination therapy of copanlisib with either chemoimmunotherapy or other target agents in hopes of improving efficacy. A multicenter phase II study [ClinicalTrials.gov identifier: NCT04263584] of copanlisib in combination with Rituximab and CHOP chemotherapy (COPA-R-CHOP) is actively enrolling patients with previously untreated DLBCL regardless of COO.

[ClinicalTrials.gov identifier: NCT03789240]

An ongoing single-institution phase II protocol of response-adapted therapy with copanlisib in combination with rituximab for untreated FL was presented at the 2020 American Society of Hematology (ASH) Annual Meeting. Investigators propose that a fixed duration of therapy will induce durable remissions. The primary endpoint is CR rate. The protocol includes a 28-day cycle of copanlisib monotherapy with 60 mg IV administered on days 1, 8, and 15. Treatment continued with six cycles of combination therapy including copanlisib 60 mg on days 1, 8, and 15 of a 28-day cycle along with rituximab 375 mg weekly $\times 4$ then on day 1 of each subsequent cycle. Patients reaching a CR discontinued treatment, while those with PR proceeded to an additional six cycles of combination copanlisib and rituximab. Preliminary results from 12 patients showed that all patients had tumor reduction with the initial cycle of copanlisib monotherapy, with a median reduction of 41%. Six patients completed the planned initial six cycles, with 67% ($n=4$) reaching a CR. Recruitment is ongoing for an enrollment goal of 65 patients. The manageable toxicity profile was similar to prior experience with no interruptions in therapy.[25] Additionally, a German-only protocol is active using the combination of copanlisib and obinutuzumab for untreated FL.

Management of AE profile

Copanlisib does carry serious AEs, some of which are unique compared with other PI3K inhibitors. The two primary AEs are infusion-related hyperglycemia and hypertension. With clinical experience and post-marketing follow up since FDA approval, the anticipated AEs are better understood and new recommendations have been formulated pertaining to the management of the toxicity profile of copanlisib. In accordance with Cheson *et al.*,[26] the most common AEs noted with copanlisib were hyperglycemia (49.3% of patients), which was grade 3 or 4 in 40% of patients. Hypertension was documented in almost 30% of patients, being grade 3 in 23.2% of patients, with no grade 4 events. Both hyperglycemia and hypertension were infusion-related and transient in nature. Diarrhea was noted in one-third of patients, but was grade 3 in only 6.3% of patients; no grade 4 diarrhea was noted. Other toxicities occurring in more than 20% of patients included neutropenia, pyrexia, fatigue, and nausea. We aim to address the management of the most common AEs.

Hyperglycemia of grade 3 and 4 was noted to be in 41% of patients but with only 2.8% being considered serious. Patients were managed conservatively with oral or intravenous (IV) fluids. The hyperglycemia was mostly transient and resolved after 24 h. Only 10% of patients were found to have a hemoglobin A1c $>6.5\%$ at the end of treatment. For nondiabetics, there is no need for post-infusion monitoring, although glucose can

be re-checked 24 h after infusion. Diabetic patients should be treated with copanlisib only following adequate glucose control, and should be monitored closely.

Grade 3 hypertension was noted in in 26% of patients treated with copanlisib monotherapy. This effect was seen after the first cycle, with blood pressure peaking 2 h after the infusion. The hypertensive period typically resolves within 24 h. Pre-existing hypertension should be recognized and treated prior to initiation of copanlisib with the goal of achieving a blood pressure less than 140/90 mmHg. In patients with resistant hypertension despite anti-hypertensive therapy, a dose reduction of copanlisib is recommended. If blood pressure remains uncontrolled despite dose reduction, copanlisib should be discontinued.

Hematologic toxicities including anemia and thrombocytopenia of grade 3 severity were noted in about 4% and 7% of patients, respectively. A complete blood count should be monitored at least weekly during treatment with copanlisib.

The most common infection noted with patients treated was pneumonia. PJP was diagnosed in 0.6% of all patients. In patients that are considered high risk, PJP prophylaxis is recommended. Patient should be monitored carefully for signs and symptoms of infection, and copanlisib should be stopped for infections of grade 3 or higher until the acute illness resolved. Of 168 patients with NHL, 21% had lower respiratory tract infections, of which 12% were grade 3 and 2% were grade 4. Noninfectious pneumonitis has been reported, with 1.9% of patients experiencing grade 3 events; there were no grade 4 events of patients undergoing copanlisib therapy. These patients were successfully managed by cessation of therapy and steroid administration.[23]

The AE profile of copanlisib was recently updated and there are no reported late-onset toxicities identified. In comparison with the similar agents in this class, copanlisib has a more favorable safety profile in respect to colitis, pneumonitis, hepatotoxicity, and infection.[15]

Future concepts

Copanlisib has shown promising results when used in combination therapies against various forms of MCL, MZL, and T-cell lymphomas. The most remarkable combination is with the BCL-2 inhibitor venetoclax. This combination is the most active in B cell lymphoma and one of the most synergistic combinations in T cell lymphomas. Copanlisib was noted to sensitize DLBCL cells to venetoclax, thus showing a synergistic effect between PI3K α/δ inhibition and BCL-2 inhibitors.[27,28] The benefit of combination therapy was also validated as there was increased induction of apoptosis in MCL and MZL primary cells in xenograft models.[28] The synergistic effect sets the stage for clinical evaluation of copanlisib and venetoclax in patients with genetically defined tumors. Exploring the potentials of combination therapies with copanlisib is a new horizon in anticancer therapy; however, the additional toxicities are also a major concern that requires careful consideration.

The pan PI3K inhibiting property of copanlisib is also being investigated in the management of PTCL and natural killer/T-cell lymphomas (NKTCL). PTCL and NKTCL are aggressive malignancies with poor prognoses and few treatment options. They demonstrate high expression of PIK3 isoforms, especially PIK3α, which is associated with low survival rate.[7] Inhibiting any single PIK3 isoform alone is not effective in the treatment of PTCL or NKTCL. It is increasingly recognized that different PIK3 isoforms have distinct expression profiles and functions in oncogenic signaling and play non-redundant roles in particular tumor types, which has prompted the development of isoform-selective inhibitors in recent years with the aim of improving efficacy, while decreasing undesirable side effects.[29] In a preclinical setting, it has been shown that copanlisib, owning to its ability to simultaneously inhibiting PIK3 α and δ, can potentially cause G0/G1 cell cycle arrest and may be a promising therapeutic agent. Copanlisib demonstrated cell cycle arrest in peripheral T cell lymphomas and natural killer T cell lymphomas, which as a result suppressed tumor growth *in vitro* and *in vivo*. This study provides evidence that inhibition of PIK3 α/δ pathway could be a promising approach for the treatment of PTCL and NKTCL.[30]

There have been a great number of pharmacologic studies trying to identify potential biomarkers that correlate with the tumor response to the PI3K inhibitors like copanlisib. A phase I study enrolled 63 patients diagnosed with lymphoma or refractory solid tumors undergoing two cycles of

copanlisib therapy at the weight-based dosing of 0.4–0.8 mg/kg. Two pharmacologic parameters were found to be correlated strongly with copanlisib plasma levels: phosphorylated AKT abbreviated by pAKT, involved in the PI3K-Akt signaling pathway, and two glucose metabolism markers: insulin and C peptide.[13] Copanlisib showed a dose-dependent suppression of pAKT and also a transient elevation of plasma glucose following copanlisib. However, there was a lack of association between these markers to individual response to treatment.[31] Gene expression profiling of the PI3K/AKT/mTOR pathway has revealed oncogenic mutations that drive prognosis across both solid and hematologic malignancies. A better understanding of tumor-specific PI3K signaling will guide treatment selection for patients most likely to respond to PI3K-targeting agents.[20,32–34]

The search continues for more reliable biomarkers to predict the clinical efficacy of copanlisib. Interleukin (IL)-6 has recently been shown to mediate resistance to PI3K pathway targeted therapy in lymphoma. It has been studied that IL-6-induced STAT3 or STAT5 activation is a critical mechanism underlying PI3K inhibitor resistance in lymphoma. STAT3 and the isoforms STAT5A/B are major parts of the Janus tyrosine kinase (JAK)/STAT pathway.[35] Cytokine assays revealed upregulation of IL-6 in both copanlisib- and duvelisib-resistant cell lines. Phosphorylated STAT5, AKT, p70S6K, and MAPK were increased in copanlisib-resistant B-cell lymphoma cells, whereas phosphorylated STAT3 and NF-κB were increased in duvelisib-resistant T-cell lymphoma cells. Previous studies have shown that STAT3 and STAT5 can serve as therapeutic targets, such as in metastatic prostate cancer, and their expression is a predictive biomarker of drug resistance in cancers.[36,37] Due to these findings, there is promise that the activation of IL-6 signaling may contribute to the PI3K resistance of B cell and T cell lymphoma cells. Combined treatment with a JAK inhibitor (BSK805) and a PI3K inhibitor showed a synergistic effect to acquired resistance to PI3K inhibitors in lymphomas.[38]

Active trials

There are a number of active clinical trials exploring the use of copanlisib alone or in combination for various hematologic malignancies. Table 1 summarizes the clinical trials using copanlisib in hematologic malignancies. The majority of these trials are in phase II. Two ongoing studies explore copanlisib monotherapy in either relapsed or rituximab-refractory indolent NHL [ClinicalTrials.gov identifier: NCT02342665, NCT02369016]. Numerous trials studying different combinations of copanlisib with standard therapy such as rituximab, or rituximab-based therapy such as CHOP or bendamustine in untreated and relapsed/refractory indolent and aggressive NHL. A wide variety of malignancies are being investigated at the current time with these combinations, including DLBCL, MZL, and CLL/SLL. Beyond B cell malignancies, one study [ClinicalTrials.gov identifier: NCT03052933] combining copanlisib and gemcitabine in relapsed/refractory PTCL is an exciting new regimen in the treatment of a disease with a very poor prognosis. Gemcitabine has been suggested as monotherapy for relapsed/refractory PTCL, though major studies were not able to reach median PFS, and the addition of a targeted agent may yield more promising results.[39]

Finally, the remaining trials explore the potential efficacy of copanlisib combined with either anti-PD1 therapy or targeted therapy. Two of these studies, [ClinicalTrials.gov identifier: NCT03484819 and NCT03877055], combine copanlisib with a newer agent like nivolumab to treat relapsed/refractory DLBCL and primary mediastinal B cell lymphoma (PMBCL) or with ibrutinib to treat MCL, respectively. The combination of copanlisib and the BCL-2 inhibitor venetoclax in treating relapsed/refractory DLBLC is being studied extensively since the discovery of their strong synergistic activity in the trial [ClinicalTrials.gov identifier: NCT04572763] (not yet recruiting as of the date of this article). The protocol evaluates the maximum tolerated dose of venetoclax when used in conjunction with copanlisib as this combination can result in several severe overlapping toxicities.[28]

Conclusion

Copanlisib is a pan-PI3K inhibitor with a tolerable toxicity profile that offers potential therapeutic benefits in numerous hematologic and solid cancers. Since FDA approval, copanlisib has seen prompt applicability into clinical practice. As monotherapy, copanlisib continues to show a promising ORR at 60.6% in indolent B cell

lymphoma after a 2-year follow up from the CHRONOS-1 trial.[15] Remarkably, the AE profile remains relatively unchanged, with the extended duration of monitoring and no evidence of cumulative toxicity. The more easily managed side effect profile of copanlisib continues to be an advantage over its two oral PI3K inhibitor predecessors, especially idelalisib, which had a number of deaths on clinical trials due to toxicities. While the weekly intravenous dosing of copanlisib may be inconvenient, the longer dosing interval allows better monitoring and control of many possible AEs that may arise.

We have reviewed the expanded use in other lymphoma subtypes including aggressive NHLs. In the case of DLBCL, copanlisib showed a modest ORR in patients with ABC subtype disease. The known role of the PI3K pathway in the ABC subtype makes inhibition a logical therapy. Copanlisib is being further studied in a number of clinical trials to evaluate for duration of response and toxicity profile over the longer follow up periods. Furthermore, copanlisib is being paired with many cytotoxic agents, immunotherapy, and newer oral chemotherapeutics in numerous ongoing trials as it has demonstrated a remarkable *in vitro* synergistic effect. Effective use of such a combination may open the door to another frontier of antitumor treatment.

While most clinical trials involving copanlisib are still ongoing, another PI3K inhibitor, alpelisib, recently received FDA approval for treatment of PI3KCA-mutant breast cancer.[40] The rapidly emerging data on targeted agents makes it imperative for the clinicians to stay up to date. Particularly to understand the differences of agents within a pharmacologic class, but also the advancing indications across malignancy subtypes.

Author contributions

All authors contributed equally to the writing and editing of the manuscript.

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References

1. Fruman DA, Chiu H, Hopkins BD, *et al*. The PI3K pathway in human disease. *Cell* 2017; 170: 605–635.
2. Yang J, Nie J, Ma X, *et al*. Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Mol Cancer* 2019; 18: 26.
3. Liu N, Rowley BR, Bull CO, *et al*. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110alpha and p110delta activities in tumor cell lines and xenograft models. *Mol Cancer Ther* 2013; 12: 2319–2330.
4. Cantley LC. The phosphoinositide 3-kinase pathway. *Science* 2002; 296: 1655–1657.
5. Srinivasan L, Sasaki Y, Calado DP, *et al*. PI3 kinase signals BCR-dependent mature B cell survival. *Cell* 2009; 139: 573–586.
6. Herman SE, Gordon AL, Wagner AJ, *et al*. Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood* 2010; 116: 2078–2088.
7. Cui W, Cai Y, Wang W, *et al*. Frequent copy number variations of PI3K/AKT pathway and aberrant protein expressions of PI3K subunits are associated with inferior survival in diffuse large B cell lymphoma. *J Transl Med* 2014; 12: 10.
8. Lannutti BJ, Meadows SA, Herman SE, *et al*. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. *Blood* 2011; 117: 591–594.
9. Tzenaki N and Papakonstanti EA. P110δ PI3 kinase pathway: emerging roles in cancer. *Front Oncol* 2013; 3: 40.
10. Majchrzak A, Witkowska M and Smolewski P. Inhibition of the PI3K/Akt/mTOR signaling pathway in diffuse large B-cell lymphoma: current knowledge and clinical significance. *Molecules* 2014; 19: 14304–14315.

11. Krause G, Hassenruck F and Hallek M. Copanlisib for treatment of B-cell malignancies: the development of a PI3K inhibitor with considerable differences to idelalisib. *Drug Des Devel Ther* 2018; 12: 2577–2590.
12. Aliqopa (copanlisib) [package insert]. Whippany, NJ: Bayer HealthCare, 2017.
13. Patnaik A, Appleman LJ, Tolcher AW, *et al.* First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann Oncol* 2016; 27: 1928–1940.
14. Dreyling M, Morschhauser F, Bouabdallah K, *et al.* Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol* 2017; 28: 2169–2178.
15. Dreyling M, Santoro A, Mollica L, *et al.* Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. *Am J Hematol.* Epub ahead of print 23 December 2019. DOI: 10.1002/ajh.25711.
16. Dreyling M, Santoro A, Mollica L, *et al.* Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol* 2017; 35: 3898–3905.
17. Dreyling M, Panayiotidis P, Egyed M, *et al.* Efficacy of copanlisib monotherapy in patients with relapsed or refractory marginal zone lymphoma: subset analysis from the CHRONOS-1 trial. *Blood* 2017; 130(Suppl. 1): 4053.
18. Dreyling M, Panayiotidis P, Follows GA, *et al.* Long-term efficacy and safety of copanlisib in multiply relapsed or refractory patients with marginal zone lymphoma. *Blood* 2019; 134: 1531.
19. Lenz G, Hawkes E, Verhoef G, *et al.* Clinical outcomes and molecular characterization from a phase II study of copanlisib in patients with relapsed or refractory diffuse large B-cell lymphoma. *Hematol Oncol* 2017; 35: 68–69.
20. Lenz G, Hawkes E, Verhoef G, *et al.* Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with molecularly defined relapsed or refractory diffuse large B-cell lymphoma. *Leukemia* 2020; 34: 2184–2197.
21. Alizadeh AA, Eisen MB, Davis RE, *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; 403: 503–511.
22. Davis RE, Ngo VN, Lenz G, *et al.* Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature* 2010; 463: 88–92.
23. Paul J, Soujon M, Wengner AM, *et al.* Simultaneous inhibition of PI3Kdelta and PI3Kalpha induces ABC-DLBCL regression by blocking BCR-dependent and -independent activation of NF-kappaB and AKT. *Cancer Cell* 2017; 31: 64–78.
24. Pongas GN, Annunziata CM and Staudt LM. PI3Kdelta inhibition causes feedback activation of PI3Kalpha in the ABC subtype of diffuse large B-cell lymphoma. *Oncotarget* 2017; 8: 81794–81802.
25. Lakhotia R, Melani C, Muppidi J, *et al.* Preliminary results from a phase II study of response-adapted therapy with copanlisib and rituximab for untreated follicular lymphoma. *Blood* 2020; 136(Suppl. 1): 39–40.
26. Cheson BD, O'Brien S, Ewer MS, *et al.* Optimal management of adverse events from copanlisib in the treatment of patients with non-Hodgkin lymphomas. *Clin Lymphoma Myeloma Leuk* 2019; 19: 135–141.
27. Bojarczuk K, Wienand K, Ryan JA, *et al.* Targeted inhibition of PI3Kalpha/delta is synergistic with BCL-2 blockade in genetically defined subtypes of DLBCL. *Blood* 2019; 133: 70–80.
28. Tarantelli C, Lange M, Gaudio E, *et al.* Copanlisib synergizes with conventional and targeted agents including venetoclax in B- and T-cell lymphoma models. *Blood Adv* 2020; 4: 819–829.
29. Rommel C, Camps M and Ji H. PI3K delta and PI3K gamma: partners in crime in inflammation in rheumatoid arthritis and beyond? *Nat Rev Immunol* 2007; 7: 191–201.
30. Huang D, Song TL, Nairismagi ML, *et al.* Evaluation of the PIK3 pathway in peripheral T-cell lymphoma and NK/T-cell lymphoma. *Br J Haematol* 2020; 189: 731–744.
31. Morschhauser F, Machiels JP, Salles G, *et al.* On-target pharmacodynamic activity of the PI3K inhibitor copanlisib in paired biopsies from patients with malignant lymphoma and advanced solid tumors. *Mol Cancer Ther* 2020; 19: 468–478.
32. Cintas C and Guillermet-Guibert J. Heterogeneity of phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin activation in cancer: is PI3K isoform specificity important? *Front Oncol* 2017; 7: 330.

33. Thorpe LM, Yuzugullu H and Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat Rev Cancer* 2015; 15: 7–24.

34. Zhang Y, Kwok-Shing Ng P, Kucherlapati M, *et al*. A pan-cancer proteogenomic atlas of PI3K/AKT/mTOR pathway alterations. *Cancer Cell* 2017; 31: 820–832.e823.

35. Wagner K-U and Schmidt JW. The two faces of Janus kinases and their respective STATs in mammary gland development and cancer. *J Carcinog* 2011; 10: 32.

36. Gu L, Dagvadorj A, Lutz J, *et al*. Transcription factor Stat3 stimulates metastatic behavior of human prostate cancer cells in vivo, whereas Stat5b has a preferential role in the promotion of prostate cancer cell viability and tumor growth. *Am J Pathol* 2010; 176: 1959–1972.

37. Mohanty SK, Yagiz K, Pradhan D, *et al*. STAT3 and STAT5A are potential therapeutic targets in castration-resistant prostate cancer. *Oncotarget* 2017; 8: 85997–86010.

38. Kim JH, Kim WS and Park C. Interleukin-6 mediates resistance to PI3K-pathway-targeted therapy in lymphoma. *BMC Cancer* 2019; 19: 936.

39. Coiffier B, Federico M, Caballero D, *et al*. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. *Cancer Treat Rev* 2014; 40: 1080–1088.

40. Piqray (alpelisib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2019.